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THE RELATION BETWEEN THE ALLERGIC INTRACUTANEOUS REACTION AND THE SYMPTOMS OF ANAPHYLAXIS*

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The intracutaneous reaction of the sensitized animal may be explained thus: The reinjection of the allergen gives rise, at the site of injection, to substances which cause an inflammatory reaction. In this way, the character of the cutaneous reaction is distinguished from the reaction obtained from intravenous reinjection in the guinea-pig, in which the main action is directed against the smooth muscle-fibers; or from that in the dog, in which the lowered blood-pressure is the prominent feature. Altho different species of animals show different symptoms on the reinjection of the allergen, and altho the same animal may show different reactions to the intracutaneous and to intravenous reinjections, it is still conceivable that the same toxin is responsible for the different results. According to this conception, the different results in the different species of animals are explained in this way: In the different species, the toxin seeks out different systems of organs on which to exercise its chief action; for example, the intravenous injections of peptone in dogs and in guinea-pigs give rise to different symptoms. In the case of the same species in which the reinjection is intracutaneous or intravenous, the explanation of the difference in results is that the same toxin gives rise to different lesions in the different organs with which it comes in contact.

On the other hand, a different conception is possible: The reinjection of allergen in different species of animals, or in the same animal, in the case of different modes of injection, leads to the formation of different toxins; the different symptoms in this event being, therefore, natural.

I have attempted to see if it is possible, by means of the intracutaneous reaction, to obtain evidence for one or other of these conceptions. The question on which the experiments were based, was this: Do guinea-pigs and rabbits give constantly a definite reaction on the

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intracutaneous injections of those poisons, or mixtures of poisons, which, on the intravenous injection in the guinea-pig, give rise to general symptoms regarded as characteristic of anaphylaxis? The poisons chosen for the experiments were: B-imidazolyl ethylamin, Witte's peptone, the toxic protein of Vaughan, and the anaphylatoxin of Friedberger.

EXPERIMENTS WITH B-IMIDAZOLYL ETHYLAMIN

The preparation¹ used was histamin hydrochlorid (Hoffmann, LaRoche Co.). Of this preparation 0.5 mg. was sufficient, on intravenous injection, to cause immediate death in a guinea-pig, weighing 500 gm. The intracutaneous injection of 0.1 c.c. of a 0.1 percent neutral solution of this preparation (0.0001 of histamin hydrochlorid) gave negative results in 11 rabbits; as did 0.1 c.c. of a 2 percent solution (0.002 gm.) in 9 rabbits. Four guinea-pigs received 0.1 c.c. of a 1 percent solution intracutaneously without a local reaction; two of these animals died within a few hours. These results confirm those of Müller,² who found that histamin does not cause a reaction on intracutaneous injection.

EXPERIMENTS WITH WITTE'S PEPTONE

Ten percent solutions of different preparations were used. Of these, 3-5 c.c., on intravenous injection, always caused death immediately, or within a few minutes, in guinea-pigs of 200-600 gm.

Pfeiffer and Mita³ obtained marked intracutaneous reactions on the injection of large amounts of Witte's peptone. The results of my experiments, in which a large number of rabbits and guinea-pigs received intracutaneous injections of 1 c.c. of the neutralized solutions, coincide with theirs. The results on the injection of smaller amounts are less definite. In the intracutaneous injection of peptone, as well as of other substances, the reaction of the solution must be considered, as the different preparations vary greatly in this respect.

One of the preparations, which was strongly alkaline, caused marked reactions in 6 rabbits on the injection of 0.1 c.c. A neutralized solution of the same preparation gave no reaction in 2 out of 3 rabbits, and a slight reaction in the third. Rabbits and guinea-pigs, on the injection of 0.1 c.c. showed, in the majority of cases, negative or very faint reactions.

EXPERIMENTS WITH THE "TOXIC PROTEIN" OF VAUGHAN

A. Preparations from egg albumin.—A guinea-pig weighing 205 gm. died within 3 hours after an intraperitoneal injection of 20 mg. of a preparation from egg albumin.

Fifteen rabbits received intracutaneous injections of 0.1 c.c. of a neutralized 4 percent solution. The majority of these showed no reactions, while, in a few, the results were doubtful. None of the fifteen gave a definite reaction.

Of 11 guinea-pigs, which received intracutaneous injections, two gave very slight reactions. The others were negative.

A second preparation was less toxic; of this, however, 50 mg. were sufficient to cause immediate death, when injected intravenously in a guinea-pig, weighing 420 gm.

1. Jour. Physiol., 1910, 40, p. 38; Ibid., 1910, 41, p. 318; Ibid., 1911, 43, p. 182.

2. Ztschr. f. Immunitätsf., 1913, 18, p. 185.

3. Ibid., 1909, 4, p. 410.

4. Jour. Infect. Dis., 1907, 4, p. 476; Ztschr. f. Immunitätsf., 1909, 1, p. 25; Jour. Am. Med. Assn., 1914, 62, p. 583.

Six rabbits were given intracutaneous injections of 1 c.c. of a neutralized 10 percent solution (i. e. 0.1 gm.). Of these, one gave a definite, tho moderate, reaction; the others showed negative, or very slight reactions.

Three guinea-pigs showed negative reactions, after 0.5 c.c. was given intracutaneously; three others showed negative, or indefinite, reactions after 1 c.c.

B. Preparations from tubercle bacilli.—I am indebted to Dr. Vaughan for this preparation. The M. L. D., on intracardial injection in guinea-pigs, was given as 0.00076 gm. A guinea-pig, weighing 340 gm., on the intravenous injection of 2 mg. in a neutralized solution, died before the end of the injection. In the calculation of the amount of the toxic protein injected, the protein not going into the solution was not considered.

Six rabbits received intracutaneous injections of 0.2 c.c. of the 10 percent neutralized solution (0.02 gm.), without showing a definite reaction. Six of the same animals received 0.5 c.c. (0.05 gm.). None gave a definite reaction. Of 7 guinea-pigs, only one gave a moderate reaction on the injection of 0.2 c.c.

EXPERIMENTS WITH FRIEDBERGER'S ANAPHYLATOXIN

A. Anaphylatoxin obtained with edestin (White and Avery).⁵—A guinea-pig, weighing 235 gm., received 3 c.c. intravenously of this preparation; after definite symptoms the animal recovered.

Four rabbits and 2 guinea-pigs received 0.1 c.c. on intracutaneous injection. No reaction was shown.

B. Anaphylatoxin from typhoid bacilli.—Müller⁶ reports his results with the intracutaneous injection of an anaphylatoxin, such as this, in normal and tuberculous guinea-pigs, without, however, giving data as to the general toxicity of the preparation. As he obtained similar slight reactions to the control injections of inactivated serum, he expresses the belief that anaphylatoxin does not possess the power to excite inflammation. With a preparation obtained by the treatment of bacilli with salt solution, he found a somewhat more definite reaction in a tuberculous animal than in a normal one.

Dold and Rados⁷ found that anaphylatoxin, obtained from bacteria, caused inflammation in the eyes of rabbits.

I made an anaphylatoxin by the treatment of dead typhoid bacilli with fresh guinea-pig serum. The intravenous injection, in a guinea-pig of 210 gm., of 2 c.c. of the fluid, obtained after centrifugation, led to slight symptoms of short duration. Six rabbits received 0.1 c.c. intracutaneously. Of these, one gave a definite reaction; two, marked reactions; and three, slight.

Fluid for control experiments was obtained by the treatment of dead bacilli with physiological salt solution. The intracutaneous injection of 0.1 c.c. of this fluid in 7 rabbits gave a marked reaction in 4 animals, a definite one in two, and a slight reaction in one. From this it may be concluded that the reactions, obtained with the anaphylatoxin, cannot be ascribed to its action. The results of the control experiment led to the discontinuation of further work with anaphylatoxin from bacteria.

C. Anaphylatoxin prepared according to the directions of Friedberger and Vallardi.⁷—This anaphylatoxin was obtained by the treatment, with fresh guinea-pig serum, of the precipitate obtained from the interaction of horse serum with the serum of rabbits immunized to horse serum. A number of different preparations were used: 1, 2, 3, 4, and 5.

5. Jour. Infect. Dis., 1913, 13, p. 103.

6. Deutsch. Med. Wchnschr., 1913, 39, p. 1492.

7. Ztschr. f. Immunitätsf., 1910, 7, p. 94.

1. The intravenous injection of 4.5 c.c. of this preparation in a guinea-pig of 210 gm. led to marked symptoms with convulsions lasting one hour; the animal recovered.

Five rabbits received 0.1 c.c. intracutaneously; three of these showed no reaction, two gave reactions. The 2 rabbits giving reactions gave equally marked positive reactions to the control injections of 0.1 c.c. normal guinea-pig serum, which they received at the same time.

Five guinea-pigs received 0.1 c.c. without any reactions.

2. The intravenous injection of 5.0 c.c., in a guinea-pig of 219 gm., led to moderate symptoms, followed by recovery.

Of 6 rabbits, each of which received 0.2 c.c. intracutaneously, five gave no reaction and one a moderate one. The injection, at the same time of 0.2 c.c. normal guinea-pig serum, gave entirely negative results.

3. The intravenous injection of 5.0 c.c. in a guinea-pig of 200 gm. caused immediate death. Six rabbits, on the intracutaneous injection of 0.2 c.c., gave no reaction.

4. The intravenous injection of 4.0 c.c. in a guinea-pig of 180 gm. led to death within a few minutes.

Six rabbits were given intracutaneous injections of 0.2 c.c.; three of these gave reactions, three did not. At the same time, these animals received 1 c.c. of normal guinea-pig serum intracutaneously; this, as in all the experiments, was treated just as was that used to prepare the anaphylatoxin, except that the addition of the precipitate was omitted. The result was that those animals that gave reactions to anaphylatoxin, also gave them to normal guinea-pig serum.

These 6 rabbits also received each 1 c.c. anaphylatoxin intracutaneously; two did not give reactions, four did. Control injections of 1 c.c. normal guinea-pig serum, as before stated, gave positive reactions in 3 of these 4 animals, while in 1 rabbit the control injection was without effect. This was the only case in all the experiments in which an animal giving a decided reaction to anaphylatoxin did not also give a reaction to normal guinea-pig serum.

Six guinea-pigs received 0.1 c.c. without giving any reaction.

5. The intravenous injection of 3.5 c.c. in a guinea-pig of 197 gm. caused immediate death.

Three rabbits received intracutaneous injections of 0.5 c.c.; two gave fairly marked reactions, and one a slight reaction. In one animal the reaction continued to increase after 24 hours, and cultures and smears showed it to be of an infectious character. I wish to note that all the anaphylatoxin and normal guinea-pig serum were obtained and kept under sterile precautions, and were proved sterile by cultures. The control injections of 0.5 c.c. normal guinea-pig serum caused reactions of the same intensity as those of the anaphylatoxin.

In the experiments with Preparations 2, 3, and 4, the same 6 rabbits were used. The experiments were carried out on February 8, 11, and 14. We see that one-half of the rabbits, which gave negative reactions to both anaphylatoxin and normal guinea-pig serum on the first injection, gave positive reactions to both on the third injection, six days later.

For Experiment 3, this is of no importance; for Experiment 4, on February 14, however, it may have to be taken into consideration. Six control animals were treated in exactly the same way with injections of guinea-pig serum. One of these animals died. Of the remaining five, one, on the fifth day, showed a marked reaction, and two, moderate reactions to 1.0 c.c. of serum, while 0.2 c.c. was without effect. Four fresh rabbits were then given intracutaneous injections of 0.1 c.c. horse serum every second day. Of these, one showed a marked

reaction as early as the third injection (on the fifth day); one at the fifth injection (on the eighth day); while the other two began to show slight reactions at the sixth injection. For Experiments 1 and 5, fresh rabbits were used.

Friedberger⁸ believes that the subcutaneous injection, even of small amounts of anaphylatoxin, easily leads to the Arthus phenomenon; he does not, however, report controls with normal guinea-pig serum. My experiments, as far as they go, hardly speak in favor of any action of anaphylatoxin causing inflammation.

The results of the experiments may be summarized thus: Primarily toxic substances, which on intravenous injection in guinea-pigs give rise to symptoms identical with, or similar to, those of anaphylaxis, given intracutaneously in guinea-pigs and rabbits, do not necessarily cause inflammation; while the sensitized animal (guinea-pig, rabbit, or dog) under certain conditions, reacts, with an inflammation, to an intracutaneous injection of the allergen. The substances giving rise to the inflammation owe their origin to an inter-reaction between the organism and the allergen.

According to the theory of Vaughan, and later of Biedl and Kraus,⁹ Friedberger,⁸ Pfeiffer,¹⁰ Schittenhelm and Weichardt,¹¹ and others, the production of the anaphylactic poisons depends on a splitting of protein; the substances used by me also derive their origin primarily from a cleavage of protein. In this respect, they are differentiated from a number of other substances, which, for example, an intravenous injection in guinea-pigs, may give rise to a distension of the lung. The possibility that they are entirely unlike the poison formed in anaphylaxis is, however, not absolutely excluded, as has been claimed by Friedberger.⁸ In proving the identity of a poison with those formed in anaphylaxis, it is often required that it should show a whole series of actions, using the symptoms observed in anaphylaxis as a criterion. This is going too far. Schittenhelm and Weichardt remark that in the process of protein splitting, during the course of which we reckon upon the appearance of the anaphylactic poisons, we must expect the formation of a number of other substances which contribute to the whole picture of anaphylaxis, while they need not participate in the principal toxic action. As examples of such concomitant features in the complex picture of anaphylaxis, there may be mentioned the

8. *Ibid.*, 1913, 18, p. 227.

9. *Ibid.*, 1911, 10, p. 711.

10. *Ibid.*, 1913, 16, p. 38; *Ibid.*, 1911, 10, p. 550; *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1912, 9, p. 409.

11. *München. med. Wehnschr.*, 1912, 59, pp. 67, 1089; *Ztschr. f. Immunitätsf.*, 1912, 14, p. 609.

increase in coagulation time of the blood and the eosinophilia, described by Schlecht,¹² which occurs in sensitized guinea-pigs, which do not die on reinjection. This idea is the more plausible, in that antianaphylactic animals also react to repeated reinjections with a marked eosinophilia. This may be ascribed to the action of the by-products of protein splitting and not to that of the principal poisons. Therefore, we must agree with Schittenhelm and Weichardt, Ahl and Schittenhelm,¹³ Vaughan, and others, that the absence of one or other of the symptoms does not necessarily speak against the identity of certain toxic substances with the poisons formed in anaphylaxis. Of course, the proof of identity rests finally on the chemical analysis.

If, however, we adopt the point of view that the substances with which I have worked, possess a close resemblance to those poisons formed on the introduction of the allergen in the circulating blood in anaphylaxis, then we are led to conclude that, in the intracutaneous reaction, the formation of substances causing inflammation comes into the foreground, and that these substances are different from those formed, for example, in the guinea-pig on intravenous injection of the allergen, and showing their action chiefly on the smooth muscles.

From the experiments of Dale,¹⁴ who worked with the isolated lung of guinea-pigs, we may conclude that the muscle takes part in the production of the poison. The results of Manwaring¹⁵ and still more, those of Voegtlin and Bernheim,¹⁶ confirmed by those of Denecke,¹⁷ also indicate that the tissues participate in the formation of the anaphylactic poisons. According to these authors, the formation of the substance causing a fall in blood-pressures in the dog does not occur without the action of the liver. The so-called cellular theory of toxin formation finds further evidence in the work of Coca,¹⁸ and of v. Fenyvessy and Freund.¹⁹ My results, also, under the supposition mentioned, seem to indicate that the tissues, in which an inflammation occurs on local injection, take part in the formation of the poisons; and that it is the difference in the tissues taking part in the formation of the poisons that causes the difference in poisons. As far as we may conclude at present, the skin does not behave differently from some

12. Arch. f. exper. Path. and Pharmacol., 1911, 67, p. 137.

13. Ztschr. f. ges. exper. Med., 1913, 1, p. 111.

14. Jour. Pharmacol. and Exper. Therap., 1912, 4, p. 167.

15. Ztschr. f. Immunitätsf., 1911, 8, p. 1.

16. Jour. Pharmacol. and Exper. Therap., 1911, 2, p. 507.

17. Ztschr. f. Immunitätsf., 1914, 20, p. 501.

18. Ibid., 20, p. 662.

19. Ibid., 22, p. 59.

other organs; for example, the lung of guinea-pigs, which, on local administration of the allergen, shows an inflammatory reaction.²⁰

However, the identity of the substances causing inflammation in the different tissues, as, for example, in skin and lungs, is not proved. It is not impossible that the skin of the sensitized animal shows certain peculiarities. I attempted to obtain some evidence on this question through the study of the course of the intracutaneous reaction in antianaphylactic guinea-pigs. It is known that large doses of horse serum, given intravenously, depress the intracutaneous reaction of the sensitized rabbit.²¹ It is to be noted, in this connection, that I found horse serum to have no influence on the intracutaneous inflammation caused by mustard oil. After a few days, however, the reactivity of the skin returns. It was my intention to determine whether the intracutaneous reaction in the guinea-pig would reappear again at a time when the animals were still resistant to the intravenous injection. As two large series of experiments, with animals of about equal weights, proved unsatisfactory on account of the extreme differences in degree of sensitization, I was obliged to give up this experiment. I found, however, a number of sensitized animals, which gave no intracutaneous reactions, altho they suffered fatal anaphylactic shock on intravenous reinjection of the allergen. Dr. Amberg tells me that similar conditions have been seen in several dogs that reacted promptly, with a marked fall in blood-pressure, to an intravenous reinjection of the allergen.

In this case, other tissue elements than the muscles seem to be involved chiefly in the formation of the poison — and this is what concerns us here.

The fact that Witte's peptone must be included among the substances causing inflammation seems to offer some difficulties to the conception. But as in the supposed splitting of protein, which underlies the formation of these poisons, reactions occur giving the freest play to all possible variations, we should not be surprised to find among the sum of split products, obtained under different conditions, a combination which contains not only the generally toxic components, but also those causing local inflammation. On the other hand, histamin and the protein poison of Vaughan, whose mother substances, at least, are split products of protein, seem to lack the power to cause inflammation. My preparations of anaphylatoxin seem also to resemble the latter substances. Still, on account of quantitative relations, I do not wish, at present, to attach too much importance to these experiments. The conception that different tissues may give rise to different split products from the same zymot presupposes the presence of different enzymatic actions. That this is no impossible condition is shown, for

20. Friedberger, *Ztschr. f. Immunitätsf.*, 1910, 7, p. 94; *Ibid.*, 1913, 18, p. 227; Ichioka, *Deutsch. Arch. f. klin. Med.*, 1912, 107, p. 500; Busson, *Wien. klin. Wchnschr.*, 1911, 24, p. 1492; Schlecht and Schwenker, *Deutsch. Arch. f. klin. Med.*, 1912, 108, p. 405; and Ströbel, *München. med. Wchnschr.*, 1912, 59, p. 1538.

21. Amberg and Knox, *Jour. Pharmacol. and Exper. Therap.*, 1912, 3, p. 223.

example, by the splitting of nucleic acid by different organs. In this case, the substance in question possesses a relatively simple constitution as compared with that of the proteins. In the normal protein metabolism in the organism we must also reckon upon a large number of enzymes; still others, as has been shown by Abderhalden and others, appear under abnormal circumstances, conditions such as prevail in the sensitized animal. It is not impossible that the split products, which we consider necessary for the anaphylactic reactions, do not arise from the allergen at all; but that the tissue protein may take part in their formation. Under such circumstances, the appearance of poisons, differing according to the tissues having part in their formation, is still more easily understood.

CONCLUSIONS

On the ground of the conception that the anaphylactic reactions are caused by substances in close relation to the parenteral splitting of protein, the experiments, detailed in this paper, speak in favor of the hypothesis that the intracutaneous reaction of the sensitized animal is *not* caused by the same split-products which lead to the general symptoms of anaphylaxis on the reinjection of the allergen into the bloodstream.